

## **REMARKS**

The present application is directed to a method of detecting anti-tumor autoantibodies in an individual by detecting complexes formed by the binding of autoantibodies in a sample from the individual with tumor marker proteins isolated from a bodily fluid obtained from a body cavity or space in which a tumor is or was present in a cancer patient. Claims 9-10, 13-14, and 19-38 were previously cancelled, and Claims 15-18 were previously withdrawn. Claims 1-8, 11, and 12 are currently under examination. Claim 1 is currently amended. Support for the amendments can be found in the specification and claims as filed such as in paragraphs [0003] and [0029] of the published specification. No new matter is introduced.

### *Rejection under 35 U.S.C. §102(b)*

Applicants thank the Examiner for the interview conducted on August 31, 2009. Examiner Bristol, John Robertson (an inventor of the present application) and Jamie Greene (applicants' representative) were present in person during the interview. As indicated on the Interview Summary prepared by the Examiner, the interview participants discussed documentation needed to complete the Information Disclosure Statements, applicants' request to defer submission of a Terminal Disclaimer, differences between the claimed method and conventional detection methods, and applicants described the differences between the claimed method and the teachings of the publication cited by the Examiner, namely Hanash *et al.* (WO 00/26668). These differences are also discussed in this Response. As also indicated on the Interview Summary prepared by the Examiner, applicants described several examples showing structure-function correlation and discussed potential claim amendments to overcome this rejection. Applicants also discussed proposed claim amendments to distinguish the claimed method over the cited Hanash *et al.* reference. Applicants have incorporated some of the proposed claim amendments discussed during the interview in this Response.

*Information Disclosure Statement*

In the Final Office Action mailed June 1, 2009, the Examiner noted that the copies of certain documents had not been received by the U.S. Patent Office with the Information Disclosure Statement filed January 13, 2009, and that therefore the citation of those documents had been stricken by the Examiner from form PTO/SB/08. Applicants will submit a copy of available documents stricken from form PTO/SB/08 with a new form PTO/SB/08. (Applicants note that the Strnad and Zeilen references are the same document. Therefore, the stricken duplicate reference will not be resubmitted.) In addition, the Examiner noted that that the Information Disclosure Statement filed April 23, 2009 was missing the appropriate PTO Form. Form PTO/SB/08 for the Information Disclosure Statement filed April 23, 2009 is enclosed.

*Rejection under 35 U.S.C. §102(b)*

The Examiner rejected Claims 1-7, 39, 41 and 44 under 35 U.S.C. §102(b) as anticipated by Hanash *et al.* (WO 00/26668, hereinafter “Hanash”). Applicants respectfully submit that the amendments to the claims overcome the rejection.

The Examiner cites page 6, lines 3-16 of Hanash for the proposition that the S100 proteins are obtained from “sera and other biological fluids”. Applicants respectfully submit that the meaning of the cited paragraph must be taken from the **context** of the document. As explained during the interview with the Examiner on August 31, 2009, this cited paragraph follows the paragraph on page 5, lines 22-29, which describes a method for the diagnosis or prognosis of cancer by **detecting** at least one of specified S100 proteins in a biological fluid sample. In this cited paragraph and two other sections cited by the Examiner at page 7, lines 3-4 and page 10, lines 10-21, Hanash is explaining that sera and other biological fluids can be used as the biological fluid sample being **tested** for the protein. Both of these two other sections of Hanash come under the heading “5.1 ASSAYS FOR DETECTION OF S100

EXPRESSION". In this section of the cited document, Hanash is **not** describing the **source** of the protein to be used in an assay.

Hanash teaches that the S100 proteins used to detect autoantibodies can be recombinantly-produced proteins (see Hanash page 11, lines 23-25) or can be isolated from cell culture using protein separation (see Hanash page 12, lines 1-2). However, Hanash **fails** to teach an immunoassay reagent containing one or more tumor marker proteins **prepared from a bodily fluid from a body cavity or space in which a tumor is or was present in one or more cancer patients** as claimed in the present application.

In the Final Office Action mailed June 1, 2009, the Examiner responded to applicants' previous arguments by noting that the pending claims did not exclude or distinguish serum obtained from the circulatory system from the claimed "body cavity or space". Applicants have **amended Claim 1** to clarify that the bodily fluid from which the tumor marker proteins are prepared is **not** a fluid derived from the systemic circulation. Support for this amendment can be found in the specification, such as paragraph [0029] of the published specification.

The Examiner further responded by noting that Examples 6 and 7 in Hanash teach solubilization of whole tissue samples. The Examiner asserted that the "solubilization cocktail" would result in a bodily fluid from a space in which a tumor is found. Applicants respectfully submit that one skilled in the art would understand that a solubilized tissue sample is **not** a bodily fluid. The term "bodily fluid" is clearly understood by reference to paragraph [0028] of the published specification, which includes fluids such as ascites, pleural effusion, seroma, hydrocoele and wound drainage fluid, as examples of bodily fluids.

In addition, the Examiner responded to applicants' previous arguments by citing page 17, lines 1-6 of Hanash as teaching that tumors secrete proteins. Applicants respectfully submit that Hanash merely teaches the use of **cultured** tumor cells to facilitate the **identification** of secretory proteins (see page 17, lines 7-12 of Hanash). Nowhere does Hanash teach that tumor marker proteins are prepared from a bodily fluid from a body cavity or space in which a tumor is or was present as claimed in the present application.

Claims 2-7, 39, 41 and 44 depend directly or indirectly from Claim 1 and contain all the limitations thereof.

In light of the foregoing remarks, applicants respectfully submit that Hanash fails to anticipate the claimed method and request withdrawal of the rejection of the claims under 35 U.S.C. §102(b).

*Double Patenting*

The Examiner maintained the provisional rejection of Claims 1-8, 11, and 12 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1, 4, and 8 of copending Application No. 10/417,633 (“the ‘633 application”) in view of Robertson *et al.* (WO 99/58978).

As mentioned previously and discussed during the interview, applicants wish to defer the filing of a terminal disclaimer in response to this rejection until allowable subject matter in the ‘633 application has been established.

*Rejection under 35 U.S.C. §112, first paragraph*

The Examiner maintained the rejection of Claims 1-8, 11, 12, and 39-44 under 35 U.S.C. §112, first paragraph, for lack of enablement. Applicants respectfully submit that the amendments to the claims overcome the rejection.

The Examiner asserts that the present application does not enable the use of the claimed methods for detecting any autoantibody against any tumor antigen for any cancer, for any neoplastic change or early carcinogenic change in asymptomatic patients, for measuring recurrence of cancer or assessing prognosis for a treatment therapy.

Claim 1 has been amended to clarify that the tumor marker proteins, prepared from the bodily fluid from a body cavity or space in which a tumor is or was present, **are over-expressed or altered forms of wild-type proteins**. Applicants note that tumor marker proteins exhibit **selective reactivity** with cancer-associated anti-tumor autoantibodies, as claimed. Support for the amendment can be found in the specification, such as in paragraph

[0003] of the published applications. Applicants respectfully submit that this amendment addresses the Examiner's concern regarding tolerance.

In addition, as explained during the interview, data set forth in the Figures of the present application describe use of the claimed methods for detecting, in a sample, autoantibody to various tumor marker antigens, such as MUC1 obtained from pleural effusion (Figures 4 and 5), MUC1 obtained from ascites (Figures 7 and 10), MUC1 obtained from wound drainage fluid and from a seroma (Figures 8 and 9), MUC16/CA125 obtained from ascites associated with an ovarian mass (Figure 6), and c-myc obtained from ascites (Figure 3).

As shown in Figure 4, antigen obtained from pleural effusion (a bodily fluid from a body cavity or space in which a tumor is or was present in one or more cancer patients) was superior over antigen obtain from urine (a bodily fluid **not** from a body cavity or space in which a tumor is or was present in one or more cancer patients) when used to detect autoantibodies to MUC1 in a cancer patient sample. In contrast, data showing that **no** difference exists between these antigens when detecting autoantibodies in a normal (control) sample is shown in Figure 5. A comparison of Figures 4 and 5 therefore shows that the antigen of the claimed method can successfully differentiate between a normal control individual and an individual predisposed to cancer. The ability of the antigen of the claimed method to achieve this level of differentiation also applies to the ability to overcome tolerance.

Figure 6 compares MUC16 obtained from the ascites fluid of a cancer patient (a bodily fluid from a body cavity or space in which a tumor is or was present in one or more cancer patients) with normal MUC16 (CA125) and shows that a sample from pre-operative patients with ovarian masses had greater reactivity with the ascites-derived MUC16 than normal MUC16 (CA125).

Figure 9 shows the superior reactivity of autoantibodies with MUC1 obtained from the seroma of patient M after cancer diagnosis over reactivity with MUC1 obtained from urine from the same individual two years before he developed cancer.

Applicants respectfully submit that the Figures of the present application show the usefulness of **several antigens** of the claimed methods (MUC1, MUC16 and c-myc) and show successful detection of **various cancers** (breast, ovarian and sarcoma) in patients, even in **asymptomatic** patients prior to cancer diagnosis.

In light of the foregoing remarks, applicants respectfully submit that the claims are enabled and request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

*Rejection under 35 U.S.C. §102(b)*

The Examiner newly rejected Claims 1-8, 11,12 and 39-44 under 35 U.S.C. §102(b) as anticipated by Robertson *et al.* (WO 99/58978, hereinafter “Robertson”). Applicants respectfully submit that the amendments to the claims overcome the rejection.

Applicants respectfully submit that the Examiner may be confusing the term “bodily fluid”, when used to described the **source** of the antigen, with the term as it is used to describe the **sample** from the cancer patient being tested. For example, page 5, lines 8-10 of Robertson describe contacting a **sample** of bodily fluids from a mammal with a panel of two or more distinct tumor marker antigens. The sample of bodily fluids is the **test sample being analyzed** in the assay, **not the source** of the antigen used in the assay. Similarly, on page 45, lines 14-15, the reference to pleural effusion, ovarian cysts and colon polyps refers to evidence of malignancies that six patients (misdiagnosed using conventional methods as being the “benign” group, but correctly diagnosed using the method taught by Robertson) were subsequently found to have. These malignancies were eventually diagnosed as lung cancer, skin cancer and adenocarcinoma. (See page 45 of Robertson, lines 7-20.)

With regard to the Examiner’s reference to Examples 1 and 2 of Robertson, applicants note that, as mentioned above, Claim 1 has been amended to clarify that the bodily fluid from which the tumor marker proteins are prepared is **not** a fluid derived from the systemic circulation.

In light of the foregoing remarks, applicants respectfully submit that Robertson fails to anticipate the claimed method and request withdrawal of the rejection of the claims under 35 U.S.C. §102(b).

### **CONCLUSION**

The foregoing is submitted as a full and complete response to the rejections in the Final Office Action mailed June 1, 2008. No additional fees are believed due, however, the Commissioner is hereby authorized to charge any deficiencies which may be required or credit any overpayment to Deposit Account Number 11-0855.

Applicants assert that the claims are in condition for allowance and respectfully request that the application be passed to issuance. If the Examiner believes that any informalities remain in the case that may be corrected by Examiner's amendment, or that there are any other issues which can be resolved by a telephone interview, a telephone call to the undersigned attorney is respectfully solicited.

Respectfully submitted,

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